

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) N.75797B GCW

Box No. I TITLE OF INVENTION	
MICROENCAPSULATED NITRIC OXIDE SYNTHASE SOURCE	
Box No. II APPLICANT	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
UNIVERSITY COLLEGE LONDON Gower Street London WC1E 9BT UNITED KINGDOM	
<input type="checkbox"/> This person is also inventor.	
Telephone No.	
Facsimile No.	
Teleprinter No.	
State (that is, country) of nationality: GB	State (that is, country) of residence: GB
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input checked="" type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
CHARLES, Ian George The Wolfson Institute for Biomedical Research The Cruciform Building University College London Gower Street London, WC1E 6BT UNITED KINGDOM	
This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality: GB	State (that is, country) of residence: GB
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	
<input checked="" type="checkbox"/> Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: <input checked="" type="checkbox"/> agent <input type="checkbox"/> common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
WOODS, Geoffrey Corlett J.A. KEMP & CO., 14 South Square, Gray's Inn, London, WC1R 5LX, United Kingdom.	
Telephone No. +44 20 7405 3292	
Facsimile No. +44 20 7242 8932	
Teleprinter No. 23676	
<input type="checkbox"/> Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

XU Weiming

The Wolfson Institute for Biomedical Research
The Cruciform Building
University College London
Gower Street
London, WC1E 6BT
UNITED KINGDOM

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
GB

State (that is, country) of residence:
GB

This person is applicant
for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

LIU, Lizhi

The Wolfson Institute for Biomedical Research
The Cruciform Building
University College London
Gower Street
London, WC1E 6BT
UNITED KINGDOM

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
GB

State (that is, country) of residence:
GB

This person is applicant
for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

☐ applicant only☐ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant
for the purposes of:

☐ all designated States☐ all designated States except the United States of America☐ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

☐ applicant only☐ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant
for the purposes of:

☐ all designated States☐ all designated States except the United States of America☐ the United States of America only☐ the States indicated in the Supplemental Box☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V	DESIGNATION OF STATES
The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):	
Regional Patent	
<input checked="" type="checkbox"/> AP	ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
<input checked="" type="checkbox"/> EA	Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
<input checked="" type="checkbox"/> EP	European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
<input checked="" type="checkbox"/> OA	OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)
National Patent (if other kind of protection or treatment desired, specify on dotted line):	
<input checked="" type="checkbox"/> AE	United Arab Emirates
<input checked="" type="checkbox"/> AG	Antigua and Barbuda
<input checked="" type="checkbox"/> AL	Albania
<input checked="" type="checkbox"/> AM	Armenia
<input checked="" type="checkbox"/> AT	Austria
<input checked="" type="checkbox"/> AU	Australia
<input checked="" type="checkbox"/> AZ	Azerbaijan
<input checked="" type="checkbox"/> BA	Bosnia and Herzegovina
<input checked="" type="checkbox"/> BB	Barbados
<input checked="" type="checkbox"/> BG	Bulgaria
<input checked="" type="checkbox"/> BR	Brazil
<input checked="" type="checkbox"/> BY	Belarus
<input checked="" type="checkbox"/> BZ	Belize
<input checked="" type="checkbox"/> CA	Canada
<input checked="" type="checkbox"/> CH and LI	Switzerland and Liechtenstein
<input checked="" type="checkbox"/> CN	China
<input checked="" type="checkbox"/> CR	Costa Rica
<input checked="" type="checkbox"/> CU	Cuba
<input checked="" type="checkbox"/> CZ	Czech Republic
<input checked="" type="checkbox"/> DE	Germany
<input checked="" type="checkbox"/> DK	Denmark
<input checked="" type="checkbox"/> DM	Dominica
<input checked="" type="checkbox"/> DZ	Algeria
<input checked="" type="checkbox"/> EE	Estonia
<input checked="" type="checkbox"/> ES	Spain
<input checked="" type="checkbox"/> FI	Finland
<input checked="" type="checkbox"/> GB	United Kingdom
<input checked="" type="checkbox"/> GD	Grenada
<input checked="" type="checkbox"/> GE	Georgia
<input checked="" type="checkbox"/> GH	Ghana
<input checked="" type="checkbox"/> GM	Gambia
<input checked="" type="checkbox"/> HR	Croatia
<input checked="" type="checkbox"/> HU	Hungary
<input checked="" type="checkbox"/> ID	Indonesia
<input checked="" type="checkbox"/> IL	Israel
<input checked="" type="checkbox"/> IN	India
<input checked="" type="checkbox"/> IS	Iceland
<input checked="" type="checkbox"/> JP	Japan
<input checked="" type="checkbox"/> KE	Kenya
<input checked="" type="checkbox"/> KG	Kyrgyzstan
<input checked="" type="checkbox"/> KP	Democratic People's Republic of Korea
<input checked="" type="checkbox"/> KR	Republic of Korea
<input checked="" type="checkbox"/> KZ	Kazakhstan
<input checked="" type="checkbox"/> LC	Saint Lucia
<input checked="" type="checkbox"/> LK	Sri Lanka
<input checked="" type="checkbox"/> LR	Liberia
<input checked="" type="checkbox"/> LS	Lesotho
<input checked="" type="checkbox"/> LT	Lithuania
<input checked="" type="checkbox"/> LU	Luxembourg
<input checked="" type="checkbox"/> LV	Latvia
<input checked="" type="checkbox"/> MA	Morocco
<input checked="" type="checkbox"/> MD	Republic of Moldova
<input checked="" type="checkbox"/> MG	Madagascar
<input checked="" type="checkbox"/> MK	The former Yugoslav Republic of Macedonia
<input checked="" type="checkbox"/> MN	Mongolia
<input checked="" type="checkbox"/> MW	Malawi
<input checked="" type="checkbox"/> MX	Mexico
<input checked="" type="checkbox"/> MZ	Mozambique
<input checked="" type="checkbox"/> NO	Norway
<input checked="" type="checkbox"/> NZ	New Zealand
<input checked="" type="checkbox"/> PL	Poland
<input checked="" type="checkbox"/> PT	Portugal
<input checked="" type="checkbox"/> RO	Romania
<input checked="" type="checkbox"/> RU	Russian Federation
<input checked="" type="checkbox"/> SD	Sudan
<input checked="" type="checkbox"/> SE	Sweden
<input checked="" type="checkbox"/> SG	Singapore
<input checked="" type="checkbox"/> SI	Slovenia
<input checked="" type="checkbox"/> SK	Slovakia
<input checked="" type="checkbox"/> SL	Sierra Leone
<input checked="" type="checkbox"/> TJ	Tajikistan
<input checked="" type="checkbox"/> TM	Turkmenistan
<input checked="" type="checkbox"/> TR	Turkey
<input checked="" type="checkbox"/> TT	Trinidad and Tobago
<input checked="" type="checkbox"/> TZ	United Republic of Tanzania
<input checked="" type="checkbox"/> UA	Ukraine
<input checked="" type="checkbox"/> UG	Uganda
<input checked="" type="checkbox"/> US	United States of America
<input checked="" type="checkbox"/> UZ	Uzbekistan
<input checked="" type="checkbox"/> VN	Viet Nam
<input checked="" type="checkbox"/> YU	Yugoslavia
<input checked="" type="checkbox"/> ZA	South Africa
<input checked="" type="checkbox"/> ZW	Zimbabwe
<input type="checkbox"/>	Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:
Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)	

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 30/7/1999 (30 July 1999)	9918076.2	GB		
item (2) 30/06/2000 (30 June 2000)	0016172.9	GB		
item (3)				
<input checked="" type="checkbox"/> The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1) & (2)				
<small>* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.</small>				
Box No. VII INTERNATIONAL SEARCHING AUTHORITY				
Choice of International Searching Authority (ISA) <small>(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):</small>		Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):		
ISA /		Date (day/month/year)	Number	Country (or regional Office)
Box No. VIII CHECK LIST; LANGUAGE OF FILING				
This international application contains the following number of sheets: request : 4 description (excluding sequence listing part) : 35 claims : 4 abstract : 1 drawings : 9 sequence listing part of description : Total number of sheets : 53		This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input type="checkbox"/> separate signed power of attorney 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input checked="" type="checkbox"/> other (specify): PF 23/77		
Figure of the drawings which should accompany the abstract:		Language of filing of the international application: ENGLISH		
Box No. IX SIGNATURE OF APPLICANT OR AGENT				
<small>Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).</small>				
_____ WOODS, Geoffrey Corlett				

For receiving Office use only	
1. Date of actual receipt of the purported international application: 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: 4. Date of timely receipt of the required corrections under PCT Article 11(2): 5. International Searching Authority (if two or more are competent): ISA /	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received: 6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	
Form PCT/RO/101 (last sheet) (July 1998; reprint January 2000)	

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET
Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's
file reference N.75797B GCW

Applicant
UNIVERSITY COLLEGE LONDON

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE £ 55 T

2. SEARCH FEE £ 605 S

International search to be carried out by
(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 53 sheets.

first 30 sheets £ 264 b1

23 x £6 = £138 b2
remaining sheets additional amount

Add amounts entered at b1 and b2 and enter total at B £402 B

Designation Fees

The international application contains all designations.

8 x £56 = £448 D

number of designation fees payable (maximum 8) amount of designation fee

Add amounts entered at B and D and enter total at I £850 I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT (if applicable) £ 44 P

5. TOTAL FEES PAYABLE £1554

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

TOTAL

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge
deposit account (see below)

☒ cheque

☐ postal money order

☐ bank draft

☐ cash

☐ revenue stamps

☐ coupons

☐ other (specify):

DEPOSIT ACCOUNT AUTHORIZATION (this mode of payment may not be available at all receiving Offices)

The RO/ ☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☐ (this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

Deposit Account No.

Date (day/month/year)

Signature

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

WOODS, Geoffrey, Corlett
J.A.Kemp & Co.
14 South Square
Gray's Inn
London WC1R 5LX
ROYAUME-UNI

J. A. KEMP & Co

REC'D - 4 DEC 2000

Action by GEO/MCE

Date of mailing (day/month/year) 22 November 2000 (22.11.00)	
Applicant's or agent's file reference N.75797B GCW	IMPORTANT NOTIFICATION
International application No. PCT/GB00/02924	International filing date (day/month/year) 28 July 2000 (28.07.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 30 July 1999 (30.07.99)
Applicant UNIVERSITY COLLEGE LONDON et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
30 July 1999 (30.07.99)	9918076.2	GB	01 Sept 2000 (01.09.00)
30 June 2000 (30.06.00)	0016172.9	GB	01 Sept 2000 (01.09.00)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Taieb Akremi
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

MCC

PCT

From the INTERNATIONAL BUREAU

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

WOODS, Geoffrey, Corlett
J.A.Kemp & Co.
14 South Square
Gray's Inn
London WC1R 5LX
ROYAUME-UNI

Date of mailing (day/month/year) 08 February 2001 (08.02.01)		IMPORTANT NOTICE	
Applicant's or agent's file reference N.75797B GCW			
International application No. PCT/GB00/02924	International filing date (day/month/year) 28 July 2000 (28.07.00)	Priority date (day/month/year) 30 July 1999 (30.07.99)	
Applicant UNIVERSITY COLLEGE LONDON et al			

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AU,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AG,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CR,CU,CZ,DE,DK,DM,DZ,EA,EE,EP,ES,
FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,
MN,MW,MX,MZ,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,
The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
08 February 2001 (08.02.01) under No. WO 01/09342

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

From the INTERNATIONAL BUREAU

To:

WOODS, Geoffrey, Corlett
J.A.Kemp & Co.
14 South Square
Gray's Inn
London WC1R 5LX
ROYAUME-UNI

A. KEMP & Co

REC'D 23 APR 2001

Action by GCW/MCC

Date of mailing (day/month/year) 11 April 2001 (11.04.01)		
Applicant's or agent's file reference N.75797B GCW		IMPORTANT INFORMATION
International application No. PCT/GB00/02924	International filing date (day/month/year) 28 July 2000 (28.07.00)	Priority date (day/month/year) 30 July 1999 (30.07.99)
Applicant UNIVERSITY COLLEGE LONDON et al		

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW

EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

National : AU, BG, CA, CN, CZ, DE, IL, JP, KP, KR, MN, NO, NZ, PL, RO, RU, SE, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

National : AE, AG, AL, AM, AT, AZ, BA, BB, BR, BY, BZ, CH, CR, CU, DK, DM, DZ, EE, ES, FI, GB,
GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW,
MX, MZ, PT, SD, SG, SI, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer:

R. Raissi

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.83.38

The demand must be filed directly with a competent International Preliminary Examining Authority. If two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EPO

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only		
Identification of IPEA		Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference N.75797B GCW
International application No. PCT/GB00/02924	International filing date (day/month/year) 28 July 2000	(Earliest) Priority date (day/month/year) 30 July 1999
Title of invention MICROENCAPSULATED NITIRIC OXIDE SYNTHASE SOURCE		
Box No. II APPLICANT(S)		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) UNIVERSITY COLLEGE LONDON Gower Street London WC1E 9BT United Kingdom		Telephone No.: Facsimile No.: Teleprinter No.:
State (that is, country) of nationality: GB	State (that is, country) of residence: GB	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) CHARLES, Ian George The Wolfson Institute for Biomedical Research The Cruciform Building University College London Gower Street London, WC1E 6BT UNITED KINGDOM		
State (that is, country) of nationality: GB	State (that is, country) of residence: GB	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) XU, Weiming The Wolfson Institute for Biomedical Research The Cruciform Building University College London Gower Street London, WC1E 6BT UNITED KINGDOM		
State (that is, country) of nationality: GB	State (that is, country) of residence: GB	
<input checked="" type="checkbox"/> Further applicants are indicated on a continuation sheet.		

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

LIU, Lizhi
The Wolfson Institute for Biomedical Research
The Cruciform Building
University College London
Gower Street
London, WC1E 6BT
UNITED KINGDOM

State (that is, country) of nationality:

GB

State (that is, country) of residence:

GB

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

☐

Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
 and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WOODS Geoffrey Corlett
 J.A. KEMP & CO.
 14 South Square
 Gray's Inn
 London
 WC1R 5LX
 United Kingdom

Telephone No.:

+44 20 7405 3292

Facsimile No.:

+44 20 7242 8932

Teleprinter No.:

23676

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION**Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☐ as originally filed

☐ as amended under Article 34

the claims ☐ as originally filed

☐ as amended under Article 19 (together with any accompanying statement)

☐ as amended under Article 34

the drawings ☐ as originally filed

☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☐ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|----------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | 1 sheets |
| 6. other (<i>specify</i>) | : | sheets |

For International Preliminary Examining Authority use only

received not received

<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. <input checked="" type="checkbox"/> fee calculation sheet | 4. <input type="checkbox"/> statement explaining lack of signature |
| 2. <input type="checkbox"/> separate signed power of attorney | 5. <input type="checkbox"/> nucleotide and or amino acid sequence listing in computer readable form |
| 3. <input type="checkbox"/> copy of general power of attorney, reference number, if any: | 6. <input type="checkbox"/> other (<i>specify</i>): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

WOODS Geoffrey Corlett

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

- | | |
|--|---|
| 3. <input type="checkbox"/> The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. | <input type="checkbox"/> The applicant has been informed accordingly. |
| 4. <input type="checkbox"/> The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5. | |
| 5. <input type="checkbox"/> Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82. | |

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. PCT/GB00/02924	For International Preliminary Examining Authority use only								
Applicant's or agent's file reference N.75797B GCW	Date stamp of the IPEA								
Applicant UNIVERSITY COLLEGE LONDON									
Calculation of prescribed fees									
1. Preliminary examination fee	EUR 1533 P								
2. Handling fee <i>(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)</i>	EUR 147 H								
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	<div style="border: 1px solid black; padding: 5px; margin-bottom: 5px;"> EUR 1680 </div> <div style="border: 1px solid black; padding: 5px; margin-bottom: 5px;"> TOTAL </div>								
Mode of Payment									
<table style="width: 100%;"> <tr> <td><input checked="" type="checkbox"/> authorization to charge deposit account with the IPEA (see below)</td> <td><input type="checkbox"/> cash</td> </tr> <tr> <td><input type="checkbox"/> cheque</td> <td><input type="checkbox"/> revenue stamps</td> </tr> <tr> <td><input type="checkbox"/> postal money order</td> <td><input type="checkbox"/> coupons</td> </tr> <tr> <td><input type="checkbox"/> bank draft</td> <td><input type="checkbox"/> other (specify):</td> </tr> </table>		<input checked="" type="checkbox"/> authorization to charge deposit account with the IPEA (see below)	<input type="checkbox"/> cash	<input type="checkbox"/> cheque	<input type="checkbox"/> revenue stamps	<input type="checkbox"/> postal money order	<input type="checkbox"/> coupons	<input type="checkbox"/> bank draft	<input type="checkbox"/> other (specify):
<input checked="" type="checkbox"/> authorization to charge deposit account with the IPEA (see below)	<input type="checkbox"/> cash								
<input type="checkbox"/> cheque	<input type="checkbox"/> revenue stamps								
<input type="checkbox"/> postal money order	<input type="checkbox"/> coupons								
<input type="checkbox"/> bank draft	<input type="checkbox"/> other (specify):								
Deposit Account Authorization <i>(this mode of payment may not be available at all IPEAs)</i> The IPEA/ <u>EPO</u> <input checked="" type="checkbox"/> is hereby authorized to charge the total fees indicated above to my deposit account. <input type="checkbox"/> <i>(this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)</i> is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.									
2805.0038 Deposit Account Number	17 January 2001 Date (day/month/year)								
Signature <u>WOODS Geoffrey Corlett</u>									

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
WOODS, Geoffrey c.
J.A. KEMP & CO.
14 South Square
Gray's Inn
London WC1R 5LX
GRANDE BRETAGNE

J. A. KEMP & Co
21 FEB 2001
Action by Bew/MCC

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year)

19.02.01

Applicant's or agent's file reference
N.75797B GCW

IMPORTANT NOTIFICATION

International application No.

PCT/GB 00/02924

International filing date (day/month/year)

28/07/2000

Priority date (day/month/year)

30/07/1999

Applicant

UNIVERSITY COLLEGE LONDON

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

22/01/2001

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

CHURCHER G

Tel. (+49-89) 2399-2545



PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

WOODS, Geoffrey c.
J.A. KEMP & CO.
14 South Square
Gray's Inn
London WC1R 5LX
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)

Date of mailing
(day/month/year) 05.11.2001

Applicant's or agent's file reference
N.75797B GCW

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/02924

International filing date (day/month/year)
28/07/2000

Priority date (day/month/year)
30/07/1999

Applicant
UNIVERSITY COLLEGE LONDON

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

 European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Hingel, W

Tel. +49 89 2399-8717



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference N.75797B GCW	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/02924	International filing date (day/month/year) 28/07/2000	Priority date (day/month/year) 30/07/1999
International Patent Classification (IPC) or national classification and IPC C12N15/53		
Applicant UNIVERSITY COLLEGE LONDON		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 22/01/2001	Date of completion of this report 05.11.2001
Name and mailing address of the international preliminary examining authority: <div style="display: flex; align-items: center;"> <div> European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 </div> </div>	Authorized officer Giebeler, K Telephone No. +49 89 2399 8546



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/02924

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-35 as originally filed

Claims, No.:

1-26 as originally filed

Drawings, sheets:

1/9-9/9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02924

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-26
	No: Claims
Inventive step (IS)	Yes: Claims 1-26
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-11, 14-26
	No: Claims 12, 13

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

R Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:
D1: WO 96 00006 A
D2: READ T -A ET AL: INTERNATIONAL JOURNAL OF DEVELOPMENTAL NEUROSCIENCE, vol. 17, no. 5/06, 1999, pages 653-663 & US 5 800 829 A
D3: WO 99 00510 A -& Invitrogen, 'T-REx System. A tetracycline-regulated expression system for mammalian cells.', version D, 1999-2000
D4: NO D. ET AL.: PROC. NATL. ACAD. SCI. USA, vol. 93, 1996, pages 3346-3351 -& WO 99 58155 A -& Invitrogen, 'Ecdysone-inducible mammalian expression system. An inducible gene expression system for mammalian cells utilizing the ecdysone analog Ponasterone A', Version E, 1998-2000
2. Novelty and inventive step is acknowledged for the subject-matter of claims 1-26. The reasons for this are as follows.
 - 2.1. The document D1, which appears to represent the closest prior art document, discloses cells containing polynucleotide constructs comprising a regulated promoter linked to a coding sequence for nitric oxide synthase (NOS). The cells are suggested for use in therapy, for instance of tumours.
 - 2.2. The polynucleotide of claim 15(a) is distinguished from those of D1 in that the promoter is responsive to ecdysone or an analog thereof. Example 6 of the application shows that microencapsulated cells containing the claimed polynucleotides plus the inducer ponasterone A inhibited the growth of cancer cells in vivo. The technical problem posed was thus the provision of polynucleotide constructs which when introduced into cells render these cells suitable for inhibition of cancer cells in vivo. Although D1 suggests the use of recombinant NOS containing cells in therapy, e.g. tumours, it could not be expected from any of the available prior art documents (see D1 and D2) that the specific construct of claim 15(a) could indeed be used for the treatment of cancer. Therefore, an inventive step is acknowledged for claim 15(a).

- 2.3. The polynucleotide of claim 15(b) is distinguished from those of D1 in that the promoter is operably linked to one or more tetracycline operator site sequence. While Figures 9 and 10 of D1 show that the maximum level of NOS expression achieved in mammalian cells using a retroviral vector was in the order of 30 nM/10⁶ cells, Figure 3 of the present application shows that levels of expression of over 100 μ M/10⁶ were achieved when using the polynucleotide construct of claim 15(b). The technical problem posed was thus the provision of nucleotide constructs suitable for the production of viable cells which express NOI and are capable of producing NO at considerably higher levels than D1. In view of the fact that cellular toxicity of NO was a known problem (see D1, page 46, line 31 to page 47, line 5), it appears that a person skilled in the art would not have reasonably expected that cells containing the claimed constructs would be viable and express NOS at such high levels. Therefore, an inventive step is acknowledged for claim 15(b).
- 2.4. Consequently, an inventive step is also acknowledged for claims 1-14 and 16-26.
3. For the assessment of the present claims 12 and 13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

4. The application does not meet the requirements of Article 6 PCT because the claims are not clear.

The term "functional variant" is unclear and meaningless in claims 1 and 15. Any expression product having nitric oxide synthase activity would anyway appear to be a nitric oxide synthase (NOS).

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**



International application No. PCT/GB00/02924

The term "analog" used in claims 1, 14, 15 and 19, which has no precise art-recognized meaning, is vague and indefinite and renders the scope of these claims unclear. Accordingly, the term "functional variant" is unclear in claim 25. The term "substantially" renders claims 4 and 5 unclear.

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference N.75797B GCW		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/02924	International filing date (day/month/year) 28/07/2000	Priority date (day/month/year) 30/07/1999	
International Patent Classification (IPC) or national classification and IPC C12N15/53			
Applicant UNIVERSITY COLLEGE LONDON			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none">I <input checked="" type="checkbox"/> Basis of the reportII <input type="checkbox"/> PriorityIII <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicabilityIV <input type="checkbox"/> Lack of unity of inventionV <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statementVI <input type="checkbox"/> Certain documents citedVII <input type="checkbox"/> Certain defects in the international applicationVIII <input checked="" type="checkbox"/> Certain observations on the international application			
Date of submission of the demand 22/01/2001		Date of completion of this report 05.11.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Giebeler, K Telephone No. +49 89 2399 8546 	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02924

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
Description, pages:

1-35 as originally filed

Claims, No.:

1-26 as originally filed

Drawings, sheets:

1/9-9/9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02924

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-26
	No: Claims
Inventive step (IS)	Yes: Claims 1-26
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-11, 14-26
	No: Claims 12, 13

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

R It m V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:
D1: WO 96 00006 A
D2: READ T -A ET AL: INTERNATIONAL JOURNAL OF DEVELOPMENTAL NEUROSCIENCE, vol. 17, no. 5/06, 1999, pages 653-663 & US 5 800 829 A
D3: WO 99 00510 A -& Invitrogen, 'T-REx System. A tetracycline-regulated expression system for mammalian cells.', version D, 1999-2000
D4: NO D. ET AL.: PROC. NATL. ACAD. SCI. USA, vol. 93, 1996, pages 3346-3351 -& WO 99 58155 A -& Invitrogen, 'Ecdysone-inducible mammalian expression system. An inducible gene expression system for mammalian cells utilizing the ecdysone analog Ponasterone A', Version E, 1998-2000
2. Novelty and inventive step is acknowledged for the subject-matter of claims 1-26. The reasons for this are as follows.
 - 2.1. The document D1, which appears to represent the closest prior art document, discloses cells containing polynucleotide constructs comprising a regulated promoter linked to a coding sequence for nitric oxide synthase (NOS). The cells are suggested for use in therapy, for instance of tumours.
 - 2.2. The polynucleotide of claim 15(a) is distinguished from those of D1 in that the promoter is responsive to ecdysone or an analog thereof. Example 6 of the application shows that microencapsulated cells containing the claimed polynucleotides plus the inducer ponasterone A inhibited the growth of cancer cells in vivo. The technical problem posed was thus the provision of polynucleotide constructs which when introduced into cells render these cells suitable for inhibition of cancer cells in vivo. Although D1 suggests the use of recombinant NOS containing cells in therapy, e.g. tumours, it could not be expected from any of the available prior art documents (see D1 and D2) that the specific construct of claim 15(a) could indeed be used for the treatment of cancer. Therefore, an inventive step is acknowledged for claim 15(a).

- 2.3. The polynucleotide of claim 15(b) is distinguished from those of D1 in that the promoter is operably linked to one or more tetracycline operator site sequence. While Figures 9 and 10 of D1 show that the maximum level of NOS expression achieved in mammalian cells using a retroviral vector was in the order of 30 nM/10⁶ cells, Figure 3 of the present application shows that levels of expression of over 100 μ M/10⁶ were achieved when using the polynucleotide construct of claim 15(b). The technical problem posed was thus the provision of nucleotide constructs suitable for the production of viable cells which express NOI and are capable of producing NO at considerably higher levels than D1. In view of the fact that cellular toxicity of NO was a known problem (see D1, page 46, line 31 to page 47, line 5), it appears that a person skilled in the art would not have reasonably expected that cells containing the claimed constructs would be viable and express NOS at such high levels. Therefore, an inventive step is acknowledged for claim 15(b).
- 2.4. Consequently, an inventive step is also acknowledged for claims 1-14 and 16-26.
3. For the assessment of the present claims 12 and 13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

4. The application does not meet the requirements of Article 6 PCT because the claims are not clear.

The term "functional variant" is unclear and meaningless in claims 1 and 15. Any expression product having nitric oxide synthase activity would anyway appear to be a nitric oxide synthase (NOS).

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/02924

The term "analog" used in claims 1, 14, 15 and 19, which has no precise art-recognized meaning, is vague and indefinite and renders the scope of these claims unclear. Accordingly, the term "functional variant" is unclear in claim 25. The term "substantially" renders claims 4 and 5 unclear.

PCT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 11 April 2001 (11.04.01)	Applicant's or agent's file reference N.75797B GCW
International application No. PCT/GB00/02924	Priority date (day/month/year) 30 July 1999 (30.07.99)
International filing date (day/month/year) 28 July 2000 (28.07.00)	
Applicant CHARLES, Ian, George et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
22 January 2001 (22.01.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer R. Raissi
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference N.75797B GCW	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 00/ 02924	International filing date (day/month/year) 28/07/2000	(Earliest) Priority Date (day/month/year) 30/07/1999
Applicant UNIVERSITY COLLEGE LONDON		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ **None of the figures.**

INTERNATIONAL SEARCH REPORT

International Application No

GB 00/02924

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/53 C12N9/02 C12N5/10 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 00006 A (UNIV PITTSBURGH) 4 January 1996 (1996-01-04) abstract page 8, line 12 - line 15 page 10, line 27 - page 11, line 2 page 11, line 27 - page 12, line 9 claims 1,6 --- -/--	1-26

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

24 October 2000

Date of mailing of the international search report

07/11/2000

Name and mailing address of the ISA

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 Fax: (+31-70) 340-3016

Authorized officer

Galli, I

INTERNATIONAL SEARCH REPORT

International Application No

P GB 00/02924

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>READ T -A ET AL: "CELLS ENCAPSULATED IN ALGINATE: A POTENTIAL SYSTEM FOR DELIVERY OF RECOMBINANT PROTEINS TO MALIGNANT BRAIN TUMOURS"</p> <p>INTERNATIONAL JOURNAL OF DEVELOPMENTAL NEUROSCIENCE, GB, PERGAMON, OXFORD, vol. 17, no. 5/06, 1999, pages 653-663, XP000882646</p> <p>ISSN: 0736-5748</p> <p>the whole document</p> <p>-& US 5 800 829 A (BROWN UNIVERSITY)</p> <p>1 September 1998 (1998-09-01)</p> <p>column 19, line 6 - line 53</p> <p>column 22, line 58 - line 65</p> <p>example 3</p>	1-26
A	<p>WO 99 00510 A (BRIGHAM & WOMENS HOSPITAL)</p> <p>7 January 1999 (1999-01-07)</p> <p>abstract</p> <p>-& Invitrogen, "T-REx System. A tetracycline-regulated expression system for mammalian cells.", version D, 1999-2000.</p> <p>XP002150947</p>	1-26
A	<p>NO D. ET AL.: "Ecdysone-inducible gene expression in mammalian cells and transgenic mice"</p> <p>PROC. NATL. ACAD. SCI. USA, vol. 93, 1996, pages 3346-3351, XP002150946</p> <p>the whole document</p> <p>-& WO 99 58155 A (THE SALK INSTITUTE)</p> <p>18 November 1999 (1999-11-18)</p> <p>-& Invitrogen, "Ecdysone-inducible mammalian expression system. An inducible gene expression system for mammalian cells utilizing the ecdysone analog Ponasterone A", Version E, 1998-2000.</p> <p>XP002150948</p>	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

P/GB 00/02924

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9600006	A	04-01-1996	US 5658565 A	19-08-1997
			AU 716623 B	02-03-2000
			AU 2869095 A	19-01-1996
			CA 2193827 A	04-01-1996
			EP 0769903 A	02-05-1997
			JP 10501989 T	24-02-1998
			US 6103230 A	15-08-2000
			US 5830461 A	03-11-1998
			ZA 9505210 A	21-02-1996
WO 9900510	A	07-01-1999	US 5972650 A	26-10-1999
			EP 0990041 A	05-04-2000

INTERNATIONAL SEARCH REPORT

Inter: and Application No

PCT/GB 00/02924

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/53 C12N9/02 C12N5/10 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	<p>WO 96 00006 A (UNIV PITTSBURGH) 4 January 1996 (1996-01-04) abstract page 8, line 12 - line 15 page 10, line 27 -page 11, line 2 page 11, line 27 -page 12, line 9 claims 1,6</p> <p style="text-align: center;">— — — — — — / —</p>	1-26



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

24 October 2000

Date of mailing of the international search report

07/11/2000

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Authorized officer

Galli, I

INTERNATIONAL SEARCH REPORT

Inter national Application No
PCT/GB 00/02924

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	<p>NO D. ET AL.: "Ecdysone-inducible gene expression in mammalian cells and transgenic mice"</p> <p>PROC. NATL. ACAD. SCI. USA, vol. 93, 1996, pages 3346-3351, XP002150946</p> <p>the whole document</p> <p>-& WO 99 58155 A (THE SALK INSTITUTE)</p> <p>18 November 1999 (1999-11-18)</p> <p>-& Invitrogen, "Ecdysone-inducible mammalian expression system. An inducible gene expression system for mammalian cells utilizing the ecdysone analog Ponasterone A", Version E, 1998-2000.</p> <p>XP002150948</p>	1-26

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter- national Application No

PCT/GB 00/02924

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9600006 A	04-01-1996	US 5658565 A	19-08-1997
		AU 716623 B	02-03-2000
		AU 2869095 A	19-01-1996
		CA 2193827 A	04-01-1996
		EP 0769903 A	02-05-1997
		JP 10501989 T	24-02-1998
		US 6103230 A	15-08-2000
		US 5830461 A	03-11-1998
		ZA 9505210 A	21-02-1996
WO 9900510 A	07-01-1999	US 5972650 A	26-10-1999
		EP 0990041 A	05-04-2000